Braasch DA, Jensen S, Liu Y, Kaur K, Arar K, White MA, Corey DR. RNA interference in mammalian cells by chemically-modified RNA. Biochemistry. 2003 Jul 8;42(26):7967-75.

Allerson CR, Sioufi N, Jarres R, Prakash TP, Naik N, Berdeja A, Wanders L, Griffey RH, Swayze EE, Bhat B. Fully 2'-modified oligonucleotide duplexes with improved in vitro potency and stability compared to unmodified small interfering RNA. J Med Chem. 2005 Feb 24;48(4):901-4.

Czauderna F, Fechtner M, Dames S, Aygun H, Klippel A, Pronk GJ, Giese K, Kaufmann J. Structural variations and stabilising modifications of synthetic siRNAs in mammalian cells. Nucleic Acids Res. 2003 Jun 1;31(11):2705-16.

Elbashir SM, Martinez J, Patkaniowska A, Lendeckel W, Tuschl T. Functional anatomy of siRNAs for mediating efficient RNAi in Drosophila melanogaster embryo lysate. EMBO J. 2001 Dec 3;20(23):6877-88

Thus, the present claims 1-3, 12, 16, 42-43, 76-78, 81, 86-88, 91, 106, 108, and 110-114 are drawn to a genus of nucleic acids that share the following common structural features: (i) they are isolated RNAs, (ii) they have the length of about 21-23 nucleotides, (iii) they have a sequence that corresponds to (claims 1-3, 43, 74-78, 81, 86-88, 91, and 108), including those that are complementary to (claim 106), a target RNA or gene and they are able to induce degradation of the target RNA by the mechanism of RNA interference (RNAi). Claims 72 74-75, 82, 84-85, 92 and 94-95 relate to isolated DNA that encodes RNA having these same properties. Applicants have therefore included sufficient structural data to define the genus of nucleic acids of the invention.

As discussed in the interview with the Examiner the pending claims are broad. However, the claims include adequate structure and the specification provides an adequate written description to support the breadth of the claims. An element of the invention is the size of the RNA. This element is included in each of the pending claims.

The invention is based on the discovery that long dsRNAs are processed into small RNAs which, in turn, mediate RNA interference. As discussed with the Examiner, much research being conducted at the time of the invention was focused on long pieces of RNA in various systems. Several references demonstrated the effect of using long double stranded RNA interference in a variety of systems and concluded that it was effective. For example, Fire et al., Nature 391, 806-

811 (1998) showed that long dsRNA triggers RNAi in *C. elegans*. Moreover, Wargelius et al, Biochem, Biophys Res Comm 263, 156-161 (1999); Xiong et al, Dev Bio.217, 394-405 (2000); and Svoboda et al, Dev 127, 4147-56 (2000) each showed that long dsRNA triggers RNAi in vertebrates (mouse, fish). If long dsRNA was to be used in mammalian systems, however, its use would be restricted to tissues where there is no IFN response (e.g., oocytes) or in some other way overcoming the IFN response. A review article by Fire (TIG, September 1999, v. 15, 9) in 1999 discusses concerns about the IFN response in mammals. For instance the first column of page 363 reads as follows:

> "From a technical perspective, one could certainly hope that RNA-triggered silencing would exist in vertebrates: this would facilitate functional genomics and might allow medical applications involving targeted silencing of 'renegade' genes. Although this hope is not ruled out by any current data, the simple protocols used for invertebrate and plant systems are unlikely to be effective. Mammals have a vehement response to dsRNA, the best-characterized component of which is a protein kinase (PKR) that responds to dsRNA by phosphorylating (and inactivating) translation factor EIF2a (Ref. 46)."

The surprising finding that small dsRNAs (e.g., from about 21 to about 23 nucleotides in length) robustly mediate RNAi circumvents the deleterious effects of the IFN response making these short RNAs particularly useful in functional genomic and therapeutic applications.

Accordingly Applicants request that the Examiner withdraw the claim rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections Under 35 U.S.C. § 102

A. Claims 76-95 have been rejected as being anticipated by the Fire et al patent (US 6,506,559). Fire et al teach nucleic acids of length of at least 25 nucleotides that mediate RNAi. In contrast, the present claims are limited to nucleic acids that are about 21-23 nucleotides in length. The Examiner has asserted that use of the term "about" used in the rejected claims is not sufficient to limit the length of the nucleotides. Applicants disagree.

Even if the term "about 23 nucleotides" could be read to mean 25 or 26 nucleotides, the recitation of a double stranded RNA of at least 25 nucleotides is not sufficient to anticipate a claim limited to a double stranded RNA of about 21 to about 23 nucleotides. Fire et al teach a class of RNA molecules of a large size range. The examples that are tested and are indicated to

be preferred are much larger than 25 nucleotides. A generic disclosure that encompasses a vast number of compounds does not describe and thus anticipate all of the compounds embraced therein. ***E.I duPont de Nemours & Co. v Ladd Comr pats (CADC 1964) 328 F2d 547, 140 USPQ 297. et al.*** The following MPEP section is pertinent:

> MPEP §2121.03 (II): Prior art which teaches a range within, overlapping, or touching the claimed range anticipates if the prior art range discloses the claimed ranged with 'sufficient specificity': "What constitutes a 'sufficient specificity' is fact dependent. If the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with 'sufficient specificity' to constitute an anticipation of the claims. The unexpected results may also render the claims unobvious. the question of 'sufficient specificity' is similar to that of 'clearly envisaging' a species from a generic teaching."

The particular facts of this case fall within the scenario outlined in MPEP §2121.03 (II). The prior art provides a broad range of RNA sizes. The teachings of the prior art as a whole suggest that larger pieces of RNA are most useful. The claims recite a very narrow range of RNA sizes that are useful. To the extent that there may be any overlap in the ranges, the prior art does not provide "sufficient specificity" that would suggest to one of skill in the art that RNA of about 21 to about 23 nucleotides would have superior activity. Additionally, the claimed invention is based on the unexpected finding that RNA within the claimed small size range are very effective in mediating RNAi. Fire et al. do not recognize or suggest this property. In fact, the references described above in the section 112 discussion demonstrate the unexpectedness of the discovery of the invention. Those of skill in the art believed that long dsRNA was required for effecting the process of RNA interference.

Additionally, new claims 113-114 have limitations which clarify that the RNA is less than 25 nucleotides in length. Such claims are clearly distinct over the prior art.

Therefore, the nucleic acid molecules described by Fire et al do not anticipate the claimed nucleic acids. Accordingly, Applicants respectfully request that the Examiner withdraw the claim rejection under 35 U.S.C. § 102.

B. Claims 1, 3-5, 12, 16, 42, 48-50, 76, 78-86, and 88-95 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Baulcombe *et al.* (US 6,531,647). Baulcombe et al describe a class of nucleic acid molecules that are referred to as fiRNA. The Baulcombe invention is carried out in plants and described to be applicable only in plants.

The pending claims have been amended to add the limitation of former claim 109, which was limited to mammalian mRNA and was not anticipated by Baulcombe et al. The methods and compositions of Baulcombe et al are limited to those in plants. Thus, each of the claims should be allowable in view of Baulcombe et al.

Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 102(e).

Summary

It is believed that the claims are in condition for allowance. A prompt and favorable action is earnestly solicited. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

By: _____

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The Examiner's arguments for a lack of written description seems to be based, at least in part, on the principle that a claim to a DNA sequence must be described in terms of a sequence of nucleotides. For example, the Examiner relies on *Fiers* (paragraph bridging pages 4 and 5). The issue in *Fiers* was whether there was support for a DNA encoding b-IF where the only structural characteristic capable of identifying the DNA was its sequence. The claimed RNA and DNA molecules have common structural features and do not need to be defined by sequence. Additionally each of 1-5, 12, 16, 43, 76-81, 86-91, and 103-109 are directed to RNA, not DNA sequences.

The Examiner has objected to the scope of the claims because of the inclusion of analogs in dependent claims 4, 79, and 89 (Office Action page 9 third full paragraph). Claims 4, 79, and 89 have been canceled and re-written as new independent claims 110 and 112. Thus, claims 1-3, 12, 16, 42-43, 72, 74-78, 81-82, 84-88, 91-92, 94-95, 106, and 108 do not encompass analogs and it is requested that the rejection on this basis be withdrawn.

New claims 110-112 include the limitation that the isolated RNA includes one or more "non-naturally occurring nucleotides or deoxyribonucleotide." Non-naturally occurring nucleotides are well-known in the art and are routinely used in DNA and RNA based methods. For instance examples of these types of nucleotides have been used in the Antisense field for years. It is not required for Applicants to include an extensive list of known substitutions (non-naturally occurring nucleotides) in the specification in order to supply an adequate written description. Such non-naturally occurring nucleotides are well known in the art.

Furthermore, many studies have confirmed, as was expected by Applicants, that the use of one or more non-naturally occurring nucleotides in RNA of about 21 to about 23 nucleotides in length is effective for accomplishing RNA interference. Examples of these studies are found in the following references, copies of which are included in the attached IDS.

Chiu YL, Rana TM. siRNA function in RNAi: a chemical modification analysis. RNA. 2003 Sep; 9 (9):1034-48

Elmen J, Thonberg H, Ljungberg K, Frieden M, Westergaard M, Xu Y, Wahren B, Liang Z, Orum H, Koch T, Wahlestedt C. Locked nucleic acid (LNA) mediated improvements in siRNA stability and functionality. Nucleic Acids Res. 2005 Jan 14 2005;33(1):439-47.

The Examiner has also indicated that the specification does not provide any evidence "whether the sequence interferes with RNA transcription or not, especially because the transcriptional start site is not disclosed." (Office Action page 9 lines 4-6.) It is not necessary for Applicant to identify the transcription start site. The issue was also discussed in the interview with the Examiner. It was concluded that the rejection applied to claims 5, 73, 80, 83, 90, and 93 that relate to transcriptional silencing but not the claims that relate to RNA interference. Claims 5, 73, 80, 83, 90, and 93 have been canceled herewith. It is believed that the cancellation is sufficient to overcome the rejection.

The language used in the claims of the present application is consistent with similar claims that have been issued in U.S. patents. For example, the Fire *et al.* (US Patent No. 6,506,559) and Baulcombe *et al.* (US Patent No. 6,531,647) patents cited in the Office Action have issued claims drawn to methods of using large genera of nucleic acids, even broader than the present claims. Neither of these genera of nucleic acids is limited by the use of SEQ ID Nos. to describe the structure of the members of the genera.

Additionally, when the facts under consideration herein are applied in the context of case law and the written description guidelines, it is clear that Applicants have provided an adequate written description for the claimed invention. A relevant inquiry in analyzing written description is whether the application "clearly allow persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed"[1] or, in other words, that the inventor was in "possession" of the invention.[2] The instant invention, as discussed above, is based on the finding that isolated RNA possessing certain structural properties (which are set forth in the claims) have the ability to interfere with target mRNA expression by having a complementary sequence that interacts with and causes cleavage of the target mRNA. This invention is adequately and completely described throughout the specification. The structural and functional properties of the claimed RNA are incorporated into the pending claims and fully described in the specification. It is clear that Applicants had possession of the complete claimed invention at the time that the application was filed and an adequate written description of the claimed invention was included in the specification.

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[1] *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).
[2] *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996).

Information Disclosure Statement

As discussed with the Examiner, Applicants hereby submit an Information Disclosure Statement (IDS) and Form 1449 citing references. Applicants request that the Examiner review the IDS including the comments therein and the references citied in the Form 1449.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 1-5, 12, 16, 42-43, and 72-95 and has rejected the new claims 103-109 under 35 U.S.C. § 112, first paragraph, for allegedly failing to satisfy the written description requirement. The Examiner alleges that the written description requirement is not satisfied because according to the Examiner the specification lacks detail on structural features of the RNA and does not provide information regarding the cleavage site of RNA (Office Action page 3 lines 1-4).

The invention is based, at least in part, on the recognition that RNA having certain particular structural features, such as a size of about 21 to about 23 nucleotides in length and sequence correspondence with a target mRNA was sufficient to induce degradation of the target mRNA by RNAi when exposed to the target mRNA/gene in a cellular system. These structural and functional properties are associated with the entire genus of claimed molecules. The genus of molecules is broad but adequately described. The invention would not be adequately captured in the claims if specific nucleotides or SEQ ID NOs. were included in the claims.

The Examiner has indicated that the specification does not provide any support regarding "the cleavage site of the mRNA to which the isolated RNA corresponds to." (Office Action page 3 lines 3-4.) It is not necessary for Applicant to identify the cleavage site of the mRNA to which the isolated RNA corresponds. The isolated RNA has sequence correspondence to the mRNA. This limitation is included within the claim. The cleavage occurs in the cell in response to administration of the isolated RNA. The issue of the cleavage site was discussed in the interview with the examiner. Although Applicants believe it is unnecessary, it was agreed that Applicants would amend the claims that refer to cleavage by indicating that cleavage of the mRNA occurred within the region of sequence correspondence with the isolated RNA. The claims have been amended accordingly. It is believed that the amendment is sufficient to overcome the rejection.

Remarks

Claim Status - Election/Restriction

Claims 1-5, 12, 16, 42-43, 72-95, and 103-109 were previously pending. Claims 1, 12, 16, 43, 72, 74-76, 81, 82, 84-86, 90, 92, and 94-95 are currently amended. Claims 4, 5, 73, 79,80, 83, 89, 90, 93, 103-105, 107, and 109 are canceled herewith. Claims 6-11, 13-15, 17-41, 44-47, 51-71, and 96-102 have been withdrawn and are also canceled herewith. New claims 110-114 have been added. No new matter is introduced.

Accordingly, claims 1-3, 12, 16, 42-43, 72, 74-78, 81-82, 84-88, 91-92, 94-95, 106, 108, and 110-114 are pending, of which claims 1, 12, 16, 42, 43, 72, 74-76, 81-82, 84-86, 91-92, 94-95, 110, and 112 are independent claims.

Claims 1, 12, 16, 43, 72, 74-76, 81, 82, 84-86, 90, 92, and 94-95 were amended to add the limitation that "the mRNA is mammalian cellular mRNA or viral mRNA". Support for the limitation is found in now canceled claim 109, withdrawn claim 19 and in the specification on the pages previously cited for claim 109 as well as page 18.

Claims 1, 43, 72, 76, 81, 82, 86, and 92 were amended to add the limitation that "cleavage is directed within the region of sequence correspondence with the isolated RNA". Support for the limitation is found in the specification on page 2.

Support for new claims 110-112 is found in now canceled claims 4, 79 and 89.

Support for new claims 113 and 114 is found within the original limitation of "about 23", which clearly encompasses an upper limit of 24 (claim 113) and 23 (claim 114).

Telephone Conference

The Applicants would like to thank the Examiner for her courtesy extended to Applicant, Dr. David Bartel and Applicants' representative Helen Lockhart during the telephone interview on May 18, 2005. The rejections under 35 USC 112 and 102 were discussed with the Examiner. Applicants presented arguments with respect to the distinction of the pending claims over the prior art and for the adequate written description. The arguments are presented below in more detail. Applicants have also incorporated the claim amendment related to the cleavage site suggested by the Examiner into claims 1, 43, 72, 76, 81, 82, 86, and 92.